
RENIN AND ALDOSTERONE IN ESSENTIAL HYPERTENSION

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SUMMARY

1. The renin–aldosterone system was studied in seventy-one selected hypertensive patients. Nine (13%) were diagnosed as having primary aldosteronism. Of the twenty-three patients who presented with a history of unprovoked hypokalaemia, the incidence of primary aldosteronism was 40%.

2. Renin and aldosterone responses to the combined stimuli of a low sodium diet and the upright posture were suppressed in patients with essential hypertension. There was no evidence that the suppression was due to abnormal adrenal function, sympathetic neuropathy, or the level of the blood pressure. The mechanism of the suppressed plasma renin activity response and its significance in the pathogenesis of hypertension are unknown.

Primary aldosteronism is characterized by hypertension, hypokalaemia, inappropriate elevation of aldosterone concentrations and low plasma renin activity (PRA). Hypertensive patients without hyperaldosteronism may also show suppression of the PRA response which normally follows sodium restriction or depletion (Channik, Aldin & Marks, 1969; Creditor & Loschky, 1967; Fishman, Kuchel, Liddle, Michelakis, Gordon & Chick, 1968; Gunnels, Grim, Robinson & Wilderman, 1967; Helmer & Judson, 1968; Jose & Kaplan, 1969; Ledingham, Bull & Laragh, 1967; Leutscher, Weinberger, Doway, Nokes, Balilcian, Brodie & Willoughby, 1969), exercise (Fasola, Martz & Helmer, 1966) and acute hypotension (Udea, Yagi & Kaneko, 1968; Kaneko, Ikeda, Takeda, Inoue & Tagawa, 1968). Although not understood, it is conceivable that the mechanism of the suppressed renin response is related to the pathogenesis of the hypertension. In the present report we describe the results of our studies of the renin–aldosterone system in patients with essential hypertension.

MATERIALS AND METHODS

Forty-seven of seventy-one patients studied were evaluated in a clinical research ward; the remaining twenty-four patients were hospitalized in a general medical ward. Antihypertensive

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medications, diuretics, and potassium supplements were discontinued 10 days to 2 weeks before evaluation except in the case of two patients with severe hypertension who were taking guanethidine. Twenty-three of the seventy-one patients presented with a history of hypokalaemia, either unprovoked or persisting for at least 2 weeks off drug therapy. All patients underwent thorough evaluation which included a complete history and physical examination, urine analysis and culture, BUN, serum creatinine, Na⁺, K⁺, Cl⁻, CO₂, plasma cortisol, 24 h urine for catecholamine excretion, 17-hydroxy- and 17-keto-steroids, chest X-ray, ECG, rapid sequence IVP, and in twenty-nine patients a renal arteriogram. The patients diagnosed as having essential hypertension had no evidence of steroid hypertension, parenchymal renal disease or unilateral renal arterial lesions. All had normal catecholamine excretion rates. The diagnosis of primary aldosteronism was based on the presence of hypertension, an elevated aldosterone excretion or secretion rate on a high sodium diet, and a low PRA following a low sodium diet and the upright posture. In addition, persistent hypokalaemia and potassium wasting, which were prevented by spironolactone therapy were usually present. The patient with the highest aldosterone excretion (studied in 1960) did not have a PRA measurement; the hypokalaemia and hyperaldosteronism, but not the hypertension, were corrected by removal of a 2 cm adrenocortical adenoma.

The patients evaluated at the clinical research centre were prescribed a 200–250 mEq of Na⁺ and 75 mEq of K⁺ diet for 5–7 days and then a 10 mEq of Na⁺ and 75 mEq of K⁺ diet for a subsequent 5–7 day period. Frequent serum and urine electrolytes were obtained on both diets. On the last few days of each diet 24 h urine samples were collected for aldosterone excretion rate determinations. In thirty-two patients aldosterone secretion was measured on the last day of the high-salt diet. Both the excretion and secretion rates were estimated by using the double-isotope technique of Kliman & Peterson (1960). Blood was drawn for PRA on the last 2 days of each diet with the patient in the supine position after an overnight fast, and then again after the patient had been in the upright position with frequent intervals of walking for 4 h. A modified Boucher method was used for the earlier patients studied (Gordon, Ferris & Mulrow, 1967a); the simpler and more sensitive technique for measurement of PRA described by Skinner (1967) was used for the later patients.

The general-medical-ward patients were studied on a regular hospital diet, and excreted over 100 mEq of Na⁺ per 24 h. None of these patients was sodium deprived. Because there was no difference in the aldosterone excretion rates between the patients studied on a measured high-sodium intake and the general-medical-ward patients, the results have been pooled. All seventy-one patients studied had at least one measurement of aldosterone. Aldosterone excretion was measured in sixty-nine patients, aldosterone secretion in thirty-two patients, and both aldosterone excretion and secretion in thirty patients. PRA was measured in all forty-seven patients on the metabolic ward and in two general-medical-ward patients.

Except for two patients with poorly controlled malignant hypertension, none of the patients studied was acutely ill, but they were admitted to the hospital for elective evaluation of asymptomatic hypertension. Only patients on the metabolic ward were subjected to sodium deprivation, and in that setting patients frequently dressed in street clothes and were free to leave the hospital for short periods of time. Many continued their usual work while in the ward. All were instructed to keep active by frequent walks.

The control subjects were normal hospital personnel, performing their usual daily activities and living at home. They were instructed to avoid strenuous physical exercise during the study
period. None was taking any medication. The high-sodium diet was either a measured 200–250 mEq of Na\(^+\) diet for 5–7 days or the subjects’ usual diet. The low-sodium diet was always a measured 10 mEq of Na\(^+\) diet for 5–7 days. All measured diets were identical with those of the hypertensive patients. 24 h urinary excretion of sodium was almost always greater than 140 mEq on the measured high salt or regular daily diets, indicating a high sodium intake, and in the range of 10 mEq or less on the low sodium diet. Adequacy of urine collection was checked by measurement of creatinine excretion. Early morning blood was drawn in the homes of seven subjects for determination of supine PRA (Boucher method) on both the high and low sodium diets.

RESULTS

Thirty-one hypertensive patients with normal aldosterone excretion on a high-sodium diet were placed on a low-sodium diet; fourteen demonstrated a suppressed renin response to the combined stimulus of the upright posture and sodium deprivation; i.e. PRA was lower than was found in any of the normal subjects who were similarly deprived of sodium. The results of the renin studies using the Skinner method are shown in Fig. 1. Of eighteen patients with essential hypertension who were subjected to a low sodium diet, seven had a suppressed PRA response following sodium deprivation and the upright posture. There was no difference between hypertensives and controls in the upright position on the high sodium diet. Similar

![Fig. 1. Plasma renin activity in the upright position in hypertensive patients and control subjects on high and low sodium diets (Skinner method). ●, Essential hypertension; ○, primary aldosteronism; M, malignant hypertension; ——, mean (excluding M and ○).](image-url)
results were obtained with the modified Boucher method (not shown in Fig. 1); seven of thirteen patients had a suppressed PRA response on the low-sodium diet, but supine and upright PRA values were not significantly different from the control subjects when the comparison was made on the high sodium intake. Suppression of renin activity could only be demonstrated after sodium deprivation and the upright posture. When the renin values after sodium deprivation and the upright posture obtained by both methods were combined, the mean PRA of the essential hypertensive patients was significantly less than that of controls \((P<0.05)\), and 45\% of essential hypertensive patients had PRA values below the lowest value of any of the control subjects.

![Fig. 2. Aldosterone excretion rates in hypertensive patients and control subjects on high and low sodium diets. \(\triangle\), Oral contraceptives; M, malignant hypertension; ---, mean (excluding \(\triangle\) and M).](image)

The results of the aldosterone measurements paralleled the renin findings. On a high sodium intake the mean aldosterone excretion rates of the general-medical and metabolic-ward patients were 13.2 and 11.8 \(\mu g/24\) h respectively \((P>0.05)\). On the high-sodium diet, whether the results of each patient group are considered separately or combined, the mean aldosterone excretion rate of the patients with essential hypertension (Fig. 2) was not significantly different from that of controls \((P>0.05)\). Four patients with 'essential' hypertension had elevated excretion rates on a high salt diet. One may have primary aldosteronism. In a second, who was taking oral contraceptives, the PRA was also elevated; both the aldosterone excretion rate and PRA reverted to normal after discontinuation of the contraceptive, although
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the hypertension persisted. Two patients had malignant hypertension (designated M), and both had elevated renin activity. Aldosterone secretion rates were measured in twenty-three essential hypertensive patients on a high-sodium diet and were not significantly different from the secretion rates of control subjects (132±14 and 92±13 SEM µg/24 h respectively; \( P > 0.05 \)).

After sodium deprivation aldosterone excretion rose significantly in both the essential hypertensive patients and the control subjects. However, as with the PRA response, the mean aldosterone response of the hypertensive patients was significantly less than that of controls (\( P < 0.01 \)). Only two hypertensive patients had excretion rates higher than the mean of the controls, and 31% had excretion rates below the lowest value of control subjects. The essential hypertensive patients with suppressed PRA responses also had lower aldosterone excretion rates on the low sodium diet than the PRA responsive patients. The mean values were 32·2±2·2 and 48·7±7·1 SEM µg/24 h respectively (\( P < 0.05 \)).

Nine patients were diagnosed as having primary aldosteronism. All had high aldosterone excretion and secretion rates. The excretion rate was only slightly responsive to changes in diet (Fig. 2). PRA was low in all eight subjects in whom it was measured. All had a history of unprovoked hypokalaemia before evaluation. On the fifth day of a 200 mEq of Na\(^+\) diet only one patient had a normal serum potassium concentration, although three other patients with primary aldosteronism had occasional serum potassium values in the normal range. On the high-sodium diet only three patients were in negative potassium balance. However, the other six patients were excreting inappropriately large amounts of potassium in view of the low serum concentrations.

The mechanism for the suppressed renin response to sodium deprivation in the patients with normal aldosterone excretion rates is not clear. There was no difference in age, sex, race or duration of hypertension between the patients in whom PRA responded normally and those in whom it was suppressed. Systolic, diastolic or mean blood pressure did not correlate with the height of the renin response (Fig. 3).

There was no evidence of enhanced mineralocorticoid activity in the PRA-suppressed patients. All were in positive potassium balance on a high sodium diet (Table 1); urinary

| TABLE 1. Serum potassium, potassium excretion, weight loss and adrenal steroid determinations in essential hypertensive patients with normal and suppressed PRA response. Values are means±SEM. None of the differences between the groups is significant (\( P > 0.05 \)) |
|---------------------------------|-----------------|-----------------|
|                                 | PRA-responsive  | PRA-suppressed  |
| Serum K\(^+\) (mEq/l)\(*\)      | 4·0±0·2         | 3·8±0·1         |
| K\(^+\) excretion\(*\) (mEq/24 h) | 58·2±3·5        | 51·6±4·2        |
| Weight loss (kg)\(\dagger\)    | 1·6±0·3         | 2·1±0·6         |
| 17-Hydroxy steroid excretion (mg/24 h) | 5·1±0·6      | 6·4±1·1         |
| 17-Ketosteroid excretion (mg/24 h) | 9·4±1·1        | 10·2±1·6        |
| 8 a.m. serum cortisol (µg/100 ml) | 13·4±1·6       | 15·8±1·8        |

* Final day of measured high-sodium diet.
\(\dagger\) During the period of dietary sodium depletion.
potassium excretion was not significantly different from PRA-responsive patients. On the low-sodium diet the mean weight loss and negative sodium balance were comparable in patients with suppressed and normal PRA responses. All patients with suppressed PRA had normal 17-hydroxy- and 17-keto-steroid excretion, and plasma cortisol was normal in the eight patients in whom it was measured. Further, two patients with suppressed PRA died and at post-mortem examination the adrenal glands were completely normal. The results of the studies in one of these patients are shown in Fig. 4. Aldosterone excretion was normal on a high-sodium diet. However, the undetectable renin concentrations and the lack of aldosterone response to a 10 mEq of Na\(^+\) diet suggested the possibility of primary aldosteronism. He was placed on a high-sodium diet and given 9-\(\alpha\)-fluorohydrocortisone, 0.5 mg orally twice daily for 4 days.

![Fig. 3. Comparison of mean blood pressure after sodium depletion with aldosterone excretion and upright PRA.](image)

On this regime, aldosterone excretion was suppressed to 5 \(\mu g/24\) h, and this lack of autonomy was a further point against the diagnosis of primary aldosteronism. Although eight of the fourteen patients with suppressed PRA had abnormal glucose tolerance, none had obvious signs or symptoms of autonomic neuropathy. None had postural hypotension, and all had normal 24 h urine catecholamine excretion rates. Five of the fourteen patients were passively tilted to 90° on a tilt table for 10 min; none had a change in EEG or blood pressure. Moreover, supine PRA was measured in seven out-patients with essential hypertension on large doses of guanethidine (50–600 mg/day). Fig. 5 shows that all seven patients had normal or elevated PRA despite significant postural hypotension. The elevated PRA may have been due to moderate sodium restriction and thiazide therapy. None had malignant hypertension or retinal haemorrhages. In addition, two hospitalized hypertensive patients on guanethidine had a normal PRA response to a 10 mEq of Na\(^+\) diet.
Fig. 4. Results of renin and aldosterone studies in a patient with suppressed PRA who had normal adrenal glands at autopsy.

Fig. 5. Upright plasma renin activity in hypertensive patients taking guanethidine (Skinner method).
Two factors that have a profound influence on renin and aldosterone production are sodium intake and physical activity. Forty-seven of the seventy-one hypertensive patients were evaluated on a clinical research ward while eating a standard high-sodium diet. The remaining twenty-four patients were hospitalized on a general medical ward and ate a regular hospital diet. Measurement of 24 h urinary sodium excretion indicated that this latter group had a liberal sodium intake and, in fact, the aldosterone excretion rates of the two groups were not significantly different. For these reasons the results of the two groups were combined. Similarly, in the control subjects measurement of 24 h urinary sodium excretion indicated the sodium intake was comparable with that of the hypertensive subjects.

The amount of physical activity performed by the various groups is difficult to quantitate. Every effort was made to keep the hospitalized patients active and, during the 4 h of upright posture, the patients continued to walk. On the other hand, the control subjects were advised to avoid excessive physical activity. Although it is conceivable that a difference in physical activity could explain the suppression of the renin–aldosterone response to sodium depletion in the hypertensive patients, this possibility seems unlikely since the values for renin and aldosterone obtained on the high-sodium diet were similar in the hypertensive and control groups.

Of seventy-one hypertensive patients studied, nine had elevated aldosterone excretion and secretion rates on a high-sodium diet and were diagnosed as having primary aldosteronism. Consequently, the incidence of primary aldosteronism in this highly selected group of patients, many of whom were studied because of provoked or unprovoked hypokalaemia, was 13%. The incidence would probably be much lower in an unselected hypertensive population. As one might anticipate, the incidence of primary aldosteronism is quite high in hypertensive patients with a history of unprovoked hypokalaemia; 40% had primary aldosteronism, which is the incidence reported by Fishman et al. (1968) in hypertensive patients with unprovoked hypokalaemia. George, Wright, Bell & Bartter (1970) suggested that the development of hypokalaemia in hypertensive patients after dietary sodium loading is helpful in making the diagnosis of primary aldosteronism. Our experience confirms this observation. Only one patient with essential hypertension was hypokalaemic after 5 days of a 200 mEq of Na\(^{+}\) diet, and only one patient with primary aldosteronism had a normal serum potassium on a similar diet. This latter finding is unexplained; his serum potassium was generally low on his usual diet.

Suppression of the PRA response to sodium depletion (i.e. PRA below that of any of the controls) was observed in 45% of hypertensive patients who had normal aldosterone excretion on a high sodium diet. Although it is possible that the difference in response was due to a difference in physical activity of the hospitalized patients compared with the control subjects, we do not think this is likely because of the efforts that were made to keep the patients active. Other investigators have reported that from 20 to 50% of essential hypertensive patients have a poor PRA response to acute or chronic sodium depletion (Channik et al., 1969; Creditor & Loschky, 1967; Fishman et al., 1968; Gunnels et al., 1967; Helmer & Judson, 1968; Jose & Kaplan, 1969; Ledingham et al., 1967; Leutscher et al., 1969).

Increased production of a mineralocorticoid other than aldosterone has been suggested as a possible mechanism for this suppressed renin response. Woods, Liddle, Michelakis & Brill
(1969) found that nine hypertensive patients with low PRA had higher exchangeable sodium values than hypertensive patients with normal PRA. Further, the low PRA patients had a greater hypotensive response to an inhibitor of adrenal steroid synthesis, aminoglutethimide, although aldosterone and deoxycorticosterone secretion rates were normal. Jose, Crout & Kaplan (1970) reported that the suppressed PRA response in hypertensive patients was associated with an expanded extracellular fluid space. During dietary sodium depletion these patients demonstrated an exaggerated urinary loss of sodium and lower aldosterone responses than hypertensive patients with a normal PRA response. It was concluded that an expanded extracellular fluid compartment, perhaps due to prolonged excessive sodium intake, might account for suppressed PRA.

Our results do not rule out the possibility of abnormal mineralocorticoid secretion or unusual sensitivity to a normal secretion, but they do imply that the blood pressure would have to be more sensitive to the putative mineralocorticoid than the potassium excretion. Our patients maintained normal serum potassium concentrations despite the stress of a high-sodium diet and there was no progression in seven patients who were re-evaluated as long as 2 years after the initial study. Further, two patients with suppressed PRA died and at post-mortem examination the adrenal glands were completely normal.

Neither do our results necessarily refute the possibility that prolonged high-sodium intake resulted in suppression of the renin–aldosterone system, although this was not apparent from the dietary history. It is possible that the measured high-sodium diet masked any differences in sodium excretion that might have existed between the suppressed and non-suppressed PRA patients when on the low-sodium diet. The amount of sodium in the hospital diet, however, is not excessive when compared with the sodium intake of healthy adults in the same locality.

Although there are reports indicating that the sympathetic nervous system modifies the renin response to sodium depletion (Bunag, Page & McCubben, 1966; Gordon, Kuchel, Liddle & Island, 1967b; Kuchel, Fishman, Liddle & Michelakis, 1967; Mogil, Itskovitz, Russell & Murphy, 1969; Vander & Luciano, 1967; Winer, Chokshi, Yoon & Freedman, 1969), none of our patients with suppressed renin activity had evidence of autonomic neuropathy. Moreover, seven patients with guanethidine-induced sympathetic blockade had normal or elevated PRA, and an additional two patients on guanethidine had a normal PRA response to sodium depletion.

Another possible explanation for the suppressed renin response is that the chronic elevation of arterial pressure inhibits juxtaglomerular cell activity. Indeed, Biava & West (1966) reported histological evidence of juxtaglomerular cell degeneration in renal biopsies from hypertensive patients. However, there was no difference in blood pressure between our patients with suppressed PRA and those with a normal PRA response. In fact, Helmer & Judson (1968) reported that patients with suppressed PRA had lower blood pressures and they found a significant positive correlation between the height of the mean blood pressure and the PRA response to dietary sodium depletion.

The lower aldosterone excretion rate after sodium deprivation in the patients with suppressed PRA may simply be a reflection of the lower renin values. However, Williams, Rose, Dluhy, McCaughn, Jagger, Hickler & Lauler (1970) reported that some patients with essential hypertension who had a normal renin response to acute volume depletion showed no elevation of aldosterone secretion, and they concluded that these patients may have had a defect in the interaction of angiotensin II with the adrenal cortex.
Our results do not define the mechanism of the suppressed renin–aldosterone response, but are presented as evidence against three frequently suggested explanations. Whatever the mechanism, it is evident that a considerable number of patients with 'essential hypertension' have a suppressed renin–aldosterone system. What this may mean in terms of the pathogenesis of the hypertension remains for future studies to determine.

REFERENCES


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